UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION,
PESTICIDES
AND
TOXIC SUBSTANCES

25/JAN/1999

MEMORANDUM

Subject: Tolerance Petition No.: 7E04920
DP Barcode: D252094
Case No: 289237

From: Eugenia McAndrew, Biologist **/s/Eugenia McAndrew**
Technical Review Branch **JCR**
Registration Division (7505C)

To: Bipin Gandhi, PM Team 05
Minor Use, Inerts and Emergency Response Branch
Registration Division (7505C)

Applicant: Novartis Crop Production, Inc.
P.O. Box 18300
Greensboro, NC 27419-8300

ACTION REQUESTED: "Please review the attached MRIDs 443874-14 thru 443874-20 for acute toxicity of cloquitocet-mexyl. Please send a copy of the review to RAB1/HED."

BACKGROUND: Novartis Crop Protection, Inc. has submitted seven acute toxicity studies for the inert ingredient, cloquitocet-mexyl, Tolerance Petition No. 7E04920. The studies MRID # 443874-14 through 443874-20 were performed at Novartis Crop Protection, Inc. in Switzerland and at Huntingdon Research Centre Ltd. in England.

RECOMMENDATIONS: The seven studies have been reviewed and are classified as acceptable. Because cloquicet-mexyl is an inert ingredient, it is not entered into the Label Review System. Based on the results of the toxicity studies reviewed in this memo, the signal word is CAUTION and the label must contain the appropriate language indicating that prolonged or frequent skin contact may cause allergic reactions in some individuals.

The acute toxicity profile for Tolerance Petition No. 7E04920 is as follows:

acute oral toxicity (rat)	III	acceptable
acute oral toxicity (mouse)	III	acceptable
acute dermal toxicity	III	acceptable
acute inhalation toxicity	III	acceptable
primary eye irritation	III	acceptable
primary skin irritation	IV	acceptable
dermal sensitization	Yes	acceptable

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100)

Product Manager: 05
MRID No.: 44387414

Reviewer: Eugenia McAndrew
Study Completion Date: April 2, 1987
Study No.: 861143

Testing Facility: Novartis Crop Protection, Inc., Stein, Switzerland
Author: Dr. H.R. Hartmann

Quality Assurance (40 CFR §160.12): Included

Test Material: Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 607001/002; Purity: 91.6%; a solid; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}ClNO_3$; Vehicle: distilled water containing 0.5% carboxymethylcellulose and 0.1% polysorbate 80
Species: Rat; albino; Tif: RAIf (SPF) hybrids of RII 1/Tif x RII 2/Tif
Age: 7-8 weeks
Weight (fasted): 162 to 212 g
Source: CIBA-Geigy LTD. Tierfarm, 4334 Sisseln, Switzerland

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: >2000mg/kg
   Females: >2000mg/kg
   Combined: >2000mg/kg
2. **The estimated LD_{50} is** >2000mg/kg
3. **Tox. Category:** III **Classification:** Acceptable

Procedure (Deviations from 870.1100): Individual body weight data was not supplied though the report states that weights were measured at start, days 7 and 14, and at death. Also, the number of animals displaying signs and symptoms of toxicity was not reported as required by the guidelines.

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	**Females**	**Combined**
2000	0/5	0/5	0/10
5000	1/4*	2/5	3/9

* one animal lost due to tracheal administration

Observations: No animals died at the 2000 mg/kg dose. At the 5000 mg/kg dose, 3 animals died: one male on day 2, one female on day 1, and one female on day 3. Signs and symptoms observed beginning at one hour after administration include dyspnea, exophthalmos (2000 mg/kg only), ruffled fur, and abnormal body position. All surviving animals appeared normal by day 13.

Gross Necropsy: No gross abnormalities were found in the 2000 mg/ kg group. In the 5000 mg/kg group, one male and two females showed hemorrhagic lungs and a hemorrhagic stomach. The small intestine of one female was dilated.

DATA REVIEW FOR ACUTE ORAL TOXICITY TESTING (870.1100)

Product Manager: 05
MRID No.: 44387415

Reviewer: Eugenia McAndrew
Study Completion Date: November 18, 1991
Study No.: 911300

Testing Facility: Novartis Crop Protection, Inc., Stein, Switzerland
Author: Dr. H.R. Hartmann

Quality Assurance (40 CFR §160.12): Included

Test Material: Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 904006; Purity: 96.7%; a solid; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}ClNO_3$; Vehicle: 0.5% (w/v) carboxymethylcellulose in 0.1% (w/v) aqueous polysorbate 80
Species: Mouse; Tif: MAG f (SPF)
Age: Young adult
Weight (fasted): 22 to 26 g
Source: CIBA-GEIGY Limited, Animal Production, Stein, Switzerland

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: >2000 mg/kg
   Females: >2000 mg/kg
   Combined: >2000 mg/kg
2. **The estimated LD_{50} is** >2000 mg/kg
3. **Tox. Category:** III **Classification:** Acceptable

Procedure (Deviations from 870.1100): Individual body weight data was not supplied though the report states that weights were measured immediately before administration and on days 7 and 14. Also, the number of animals displaying signs and symptoms of toxicity was not reported as required by the guidelines. These deviations did not affect the outcome of the study.

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

Observations: No animals died during the study. Signs and symptoms observed beginning at one hour after exposure include dyspnea, piloerection, and hunched posture. All animals appeared normal by day 4
.
Gross Necropsy: No gross abnormalities were found.

DATA REVIEW FOR ACUTE DERMAL TOXICITY TESTING (870.1200)

Product Manager: 05
MRID No.: 44387416

Reviewer: Eugenia McAndrew
Study Completion Date: April 30, 1987
Study No.: 861147

Testing Facility: Novartis Crop Protection, Inc., Stein, Switzerland
Author: Dr. H.R. Hartmann

Quality Assurance (40 CFR §160.12): Included

Test Material: Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 607001/002; Purity: 91.6%; a solid; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}ClNO_3$; Vehicle: distilled water containing 0.5% carboxymethylcellulose and 0.1% polysorbate 80
Species: Rat; albino; Tif: RAIf (SPF) hybrids of RII 1/Tif x RII 2/Tif
Age: 7-8 weeks
Weight: 210 to 254 g
Source: CIBA-GEIGY LTD. Tierfarm, 4334 Sisseln, Switzerland

Dermal LD_{50} Testing:

Conclusion:

1. **LD_{50} (mg/kg):**
   Males: >2000 mg/kg
   Females: >2000 mg/kg
   Combined: >2000 mg/kg
2. **The estimated LD_{50} is** >2000 mg/kg
3. **Tox. Category:** III **Classification:** Acceptable

Procedure (Deviations from 870.1200): Individual body weight data was not supplied though the report states that weights were measured at start and on days 7 and 14. Also, the number of animals displaying signs and symptoms of toxicity was not reported as required by the guidelines. These deviations did not affect the outcome of the study.

Results:

Dosage (mg/kg)	Number of Deaths/Number Tested		
	Males	Females	Combined
2000	0/5	0/5	0/10

Observations: No animals died during the study. Signs and symptoms observed beginning at one hour after exposure include dyspnea, ruffled fur, and abnormal body positions. All animals appeared normal by day 12.
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Gross Necropsy: No gross abnormalities were found.

DATA REVIEW FOR ACUTE INHALATION TOXICITY TESTING (870.1300)

Product Manager: 05
MRID No.: 44387417

Reviewer: Eugenia McAndrew
Study Completion Date: June 5, 1987
Study No.: CBG 435/87744

Testing Facility: Huntingdon Research Centre Ltd., England
Author: Graham C. Jackson, B.A., L.R.S.C.

Quality Assurance (40 CFR §160.12): Included

Test Material: Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 607001/2; Purity: 91.6%; a beige powder; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}ClNO_3$;
Species: Rat; albino; WISTAR
Age: Males: about 7 weeks; Females: about 9 weeks
Weight: Males: 184 to 199 g; Females: 220 to 241 g
Source: Interfauna U.K. Ltd., England

Conclusion:

1. **LC_{50} (mg/L):**
   Males: >0.935 mg/L
   Females: >0.935 mg/L
   Combined: >0.935 mg/L
2. **The estimated LC_{50} is** >0.935 mg/L
3. **Tox. Category:** III **Classification**: Acceptable

Procedure (Deviations from 870.1300): None

Exposure Concentration mg/L (Analytically Determined)	Number of Deaths/Number Tested		
	Males	Females	Combined
.935	1/5	0/5	1/10

Clinical Observations: One rat died within ten minutes of the end of exposure. According to the report: "The death of this rat could be attributed to the method of constraint but the possibility that the death resulted from exposure to CGA 185072 cannot be excluded." All rats experienced exaggerated respiratory movements during the last two hours of exposure which persisted for up to two days post exposure. All surviving rats were lethargic upon removal from the exposure chamber only. Other clinical signs include brown staining around the snout and jaws in male rats and over the whole body in female rats visible for 3 days, yellow staining in urogenital region in males for 2 days, and partial closing of the eyes in males upon removal from the chamber. All rats were normal in appearance and behavior by day 4. There were no effects on body weight associated with exposure.

Necropsy Findings: There were no macroscopic abnormalities in the rats that survived the exposure. The stomach of the rat that died was distended with gas.

Chamber Atmosphere		
Analytical conc. (mg/L)	**MMAD[a]**	**GSD[b]**
0.935	72% of particles were 5.5 µm or less in aerodynamic diameter	--

[a] The average MMAD was not reported.
[b] GSD was not reported.

Chamber Environment[c]	
Chamber Volume	50 L
Airflow	25 LPM
Temperature	23.2^0C
Relative Humidity	28%

[c]Nose only

DATA REVIEW FOR PRIMARY EYE IRRITATION TESTING (870.2400)

Product Manager: 05
MRID No.: 44387418

Reviewer: Eugenia McAndrew
Study Completion Date: March 30, 1987
Study No.: 861144

Testing Facility: Novartis Crop Protection, Inc., Stein, Switzerland
Author: Dr. M. Schoch

Quality Assurance (40 CFR §160.12): Included

Test Material: Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 607001/002; Purity: 91.6%; a solid; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}ClNO_3$;
Dosage: 0.1mL (40 mg**)**
Species: Rabbit; albino, New Zealand white (males)
Age: Approximately 12-14 weeks
Weight: 2.180 to 2.550 kg
Source: Kleintierfarm Madoerin AG, CH-4414 Fuellinsdorf
Conclusion:

1. **Toxicity Category:** III
2. **Classification**: Acceptable

Procedure (Deviations from 870.2400): None

Washed eyes:

Observations	Number "positive"/number tested				
	Hours				Days
	1	24	48	72	7
Corneal Opacity	1/3	3/3	3/3	0/3	0/3
Iritis	0/3	0/3	0/3	0/3	0/3
Conjunctivae:					
Redness*	0/3	3/3	2/3	0/3	0/3
Chemosis*	2/3	0/3	0/3	0/3	0/3
Discharge*	--	--	--	--	--

* Score of 2 or more required to be considered "positive."
– Not reported

Summary: At one hour after installation, 1/3 eyes showed corneal opacity and 2/3 eyes showed chemosis. By 24 hours, 3/3 eyes showed corneal opacity and redness. All irritation cleared by 72 hours.

DATA REVIEW FOR PRIMARY DERMAL IRRITATION TESTING (870.2500)

Product Manager: 05
MRID No.: 44387419

Reviewer: Eugenia McAndrew
Study Completion Date: March 6, 1987
Study No.: 861145

Testing Facility: Novartis Crop Protection, Inc., Stein, Switzerland
Author: Dr. M.Schoch

Quality Assurance (40 CFR §160.12): Included

Test Material: Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 607001/002; Purity: 91.6%; a solid; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}CINO_3$; Vehicle: distilled water containing 0.5% carboxymethylcellulose and 0.1% polysorbate 80
Dosage: 0.5 g
Species: Rabbit; albino, New Zealand white (males)
Age: Approximately 12-14 weeks
Weight: 2.190 to 2.320 kg
Source: Kleintierfarm Madoerin AG, CH-4414 Fuellinsdorf

Conclusion:

1. **Toxicity Category:** IV
2. **Classification**: Acceptable

Procedure (Deviations from 870.2500):

Results: PDII = .4. At one hour after patch removal, 3/3 test sites showed grade 1 erythema. All irritation cleared by 48 hours.

DATA REVIEW FOR DERMAL SENSITIZATION TESTING (870.2600)

Product Manager: 05
MRID No.: 44387420

Reviewer: Eugenia McAndrew
Study Completion Date: August 17, 1987
Study No.: 861148

Testing Facility: Novartis Crop Protection, Inc., Stein, Switzerland
Author: Dr. M. Schoch

Quality Assurance (40 CFR §160.12): Included

Test Material: Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 607001/2; Purity: 91.6%; a beige powder; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}ClNO_3$;
a 0.1% solution of CGA 185072 in 20% propylene glycol and 80% physiological saline
Positive Control Material: Paraphenylene-diamine or Potassium-dichromate
Species: Guinea pig; albino; Pirbright White Strain (Tif: DHP)
Age: Approximately 10 weeks old
Weight: 300 to 398 g
Source: Animal Production, CIBA-GEIGY, Stein, Switzerland
Method: Mauer Optimization Test

Conclusion:

1. **This product is a dermal sensitizer**.
2. **Classification**: Acceptable

Procedure (Deviations from 870.2600): None

Procedure: For the three week induction period, 20 test animals received one injection every second day to a total of 10 intracutaneous injections of a 0.1% solution of CGA 185702 in 20% propylene glycol and 80% physiological saline. The 20 control animals were treated with the vehicle alone. During the second and third week of induction, the test material was incorporated in a mixture of the normal vehicle with complete Bacto adjuvant. Fourteen days after the last sensitizing injection, the animals received a challenge injection of the test solution. Reactions were scored 24 hours after each injection during the first week of induction and 24 hours after the challenge injections. Ten days after the intracutaneous challenge injection, a subirritant dose of the test compound in 1% vaseline and vaseline alone was applied to the test animals epicutaneously under occlusive dressings and left in place for 24 hours for the epicutaneous challenge. The control group was treated with vaseline and with CGA 185072 in vaseline. Reactions were evaluated 24 and 48 hours after removing the dressings.

Results: No significant difference between the test and the control groups was seen after intradermal challenge application. After epidermal challenge application, 0/20 positive reactions were seen in the control group and 20/20 positive reactions in the test group. Therefore, CGA 185072 is classified as a dermal sensitizer. The report states that the sensitivity of the guinea pig strain is controlled every six months with paraphenylene-diamine or potassium-dichromate. However, these positive control studies were not included in the report.

ACUTE TOX ONE-LINERS

1. **DP BARCODE:** D252094
2. **PC CODE:** Inert ingredient
3. **CURRENT DATE:** 25/JAN/1999
4. **TEST MATERIAL:** Common name: CGA 185072 (cloquinocet); IUPAC Chemical Name: 2-heptyl-5-chloro-8-quinolinoxy-acetate; Batch No. P. 607001/002 and Purity: 91.6%; (except for oral study in mouse Batch No. P. 904006, 96.7%); a solid; CAS Registry Number: 99607-70-2; Molecular Formula: $C_{18}H_{22}ClNO_3$

Study/Species/Lab Study #/Date	MRID	Results	Tox. Cat.	Core Grade
Acute oral toxicity/rat Novartis Crop Protection, Inc 861143/4-2-87	44387414	LD_{50} >2000 mg/kg (males, females combined)	III	A
Acute oral toxicity/mouse Novartis Crop Protection, Inc. 911300/11-18-91	44387415	LD_{50} >2000 mg/kg (males, females combined)	III	A
Acute dermal toxicity/rat Novartis Crop Protection, Inc. 861147/4-30-87	44387416	LD_{50} >2000 mg/kg (males, females combined)	III	A
Acute inhalation toxicity rat/Huntingdon Research Centre Ltd./CBG 435/87744/6-5-87	44387417	LC_{50} > 0.935 mg/L (males, females combined)	III	A
Primary eye irritation rabbit/Novartis Crop Protection, Inc./861144/3-30-87	44387418	Corneal opacity observed in 1/3 eyes at one hour and 3/3 eyes at 24 and 48 hours. All irritation cleared by 72 hours.	III	A
Primary dermal irritation rabbit/Novartis Crop Protection, Inc./861145/3-6-87	44387419	PDII = .4. All irritation cleared by 48 hours.	IV	A
Dermal sensitization guinea pig/Novartis Crop Protection, Inc.,/861148/8-17-87	44387420	Sensitizer	–	A

Core Grade Key: **A =Acceptable, S = Supplementary, U = Unacceptable, V = Self Validated**